

In re: Anson et al.
Serial No.: PCT/GB00/03568
Filed: September 18, 2000
Page 2 of 11

IN THE CLAIMS:

Please enter the amended claims as follows:

2. (Amended) The E2NT dimer protein of Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.
3. (Amended) The E2NT dimer protein of Claim 1, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.
4. (Amended) The E2NT dimer protein of Claim 3 comprising three clusters.
5. (Amended) The E2NT dimer protein of Claim 3 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues: Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.
6. (Amended) The E2NT dimer protein of Claim 3, wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.
7. (Amended) The E2NT dimer protein of Claim 3, wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues: Pro106, Lys111, Phe168, Trp134.
8. (Amended) The E2NT dimer protein of Claim 1, further comprising residues associated with transactivation and/or replication properties of E2.
9. (Amended) The E2NT dimer of Claim 8, wherein the residues comprise any one or more of the following residues: Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

In re: Atkinson et al.
Serial No.: PCT/GB00/03568
Filed: September 18, 2000
Page 3 of 11

10. (Amended) A method for determining the structure of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, wherein the E2NT dimer protein and any of its mutations are mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. (Amended) The method according to Claim 10 in rationalised antiviral drug design.

12. (Amended) A method for identifying and/or selecting a candidate therapeutic agent, the method comprising:

determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2 *in vitro*.

13. (Amended) The method according to Claim 12 further comprising identifying and/or selecting an antiviral candidate therapeutic agent.

14. (Amended) The method according to Claim 13, wherein the identifying and/or selecting of the antiviral candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. (Amended) A method of treating an HPV infection in a subject comprising: introducing an E2NT dimerisation inhibitor in said subject.

16. (Amended) The method according to Claim 15 further comprising treating warts, proliferative skin lesions and/or cervical cancer.

18. (Amended) Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to

Claim 1 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

20. (Amended) The method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. (Amended) The method of claim 19, wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. (Amended) The method of Claim 19, wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. (Amended) The method of Claim 19, wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

32. (Amended) A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3 or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and
- b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

In re: Arison et al.
Serial No.: PCT/GB00/03568
Filed: September 18, 2000
Page 5 of 11

Please cancel claim 33 without prejudice or disclaimer.

Please add the following new claims:

34. (New) A method for designing a potential antiviral compound for the prevention or treatment of an HPV infection, comprising:

a) obtaining crystals of the E2NT dimer protein such that the three dimensional structure of the crystallized E2NT dimer protein can be determined to a resolution of about 1.9 Å or better,

b) evaluating the three dimensional structure of the crystallized E2NT dimer protein;

c) synthesizing the potential antiviral compound based on the three-dimensional crystal structure of the crystallized E2NT dimer protein;

d) contacting an HPV virus with the potential antiviral compound; and

e) assaying the HPV virus for infectivity or monitoring the virus for activity, or both, whereby a decrease in the infectivity of the virus or a change in the activity of the virus indicates the compound may be used for the prevention or treatment of an HPV infection.

35. (New) The method according to claim 34, wherein the antiviral compound is a peptide or polypeptide.

36. (New) The method according to claim 34, wherein the E2 N-terminal module dimer protein or homologue thereof comprises residues vital for transcriptional and replication activities of said protein.

In re: A. [REDACTED] et al.
Serial No.: PCT/GB00/03568
Filed: September 18, 2000
Page 6 of 11

37. (New) The method according to claim 36, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

38. (New) The method according to claim 37, wherein said E2NT dimer protein comprises three clusters.

39. (New) A method for designing a candidate compound for screening for binding to or inhibition of an HPV infection, comprising:

a) utilizing the three dimensional structure of a crystallized E2NT module dimer protein wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer; and

b) designing a candidate binding compound based on the three-dimensional crystal structure of the crystallized E2NT dimer protein for binding to said dimer protein.

40. (New) The method of claim 39, wherein the candidate compound is a peptide or polypeptide.

41. (New) A method for determining the crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, wherein the E2NT dimer protein and any of its mutations is mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.